Update on Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the U.S.

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Data from the Women and Infants Transmission Study for the period 1990-1999 clearly indicate a decreasing rate of mother-to-infant transmission as an increasing percentage of pregnant women received ZDV monotherapy and, increasingly in more recent years, multi-regimen antiretroviral therapy (multi-ART) or highly active antiretroviral therapy (HAART). In 1990 with less than 5% of HIV-infected pregnant women in the study on ZDV monotherapy (prior to the introduction of the prophylactic regimen documented by PACTG 076), the transmission rate was 22.7 per 100 live births. In 1999, with more than 95% of pregnant women in the study on some form of antiretroviral therapy, the rate was 3.3 per 100 live births.

Public Health Service guidelines for reducing vertical transmission of HIV were first published in 1994, within 6 months of the presentation of PACTG 076 results. The latest *printed* guidelines appeared in a January 30, 1998 *MMWR Recommendations and Reports*. Since 1999, a perinatal HIV guidelines working group, consisting of outside consultants as well as PHS representatives, have reviewed the latest data and developed updates to the guidelines through a monthly conference call. Updates are posted continuously on the HIV/AIDS Treatment Information Service website (www.hivatis.org), sponsored by several HHS agencies.

Today I will present the major updates to the guidelines since their publication in the 1998 *MMWR*. Briefly stated, they include:

- addition of a section on preconception counseling
- update on mitochondrial toxicity issues in pregnancy and in utero antiretroviral exposure
- recommends HAART if HIV RNA >1,000 (can discontinue postpartum)
- addition of NVP if RNA+ at delivery is **not** recommended
- resistance testing same as for non-pregnant women
- recommendations for intrapartum/postpartum regimens
- ARV administered >48 hours postpartum only to newborn is unlikely to be effective
- elective cesarean section for reducing transmission.

Preconceptional Counseling and Care for HIV-Infected Women of Childbearing Age: What Should Be Discussed *Before* Pregnancy

Before pregnancy, the following counseling and care should be provided to HIV-infected women of childbearing age:

- contraception to reduce unintended pregnancy (well over 50% of pregnancies in the U.S. are

unintended)
- counseling re: perinatal transmission and prevention
- initiate/modify ARV therapy before conception
    - avoid drugs with possible reproductive toxicity
    - choose drugs effective in reducing perinatal transmission
    - attain stable, maximally suppressed viral load
    - evaluate/treat ARV side effects that could effect maternal-fetal outcome (hyperglycemia, hepatic toxicity, anemia)
- evaluate OIs, need for prophylaxis, immunizations
- optimize nutritional status
- standard (history, STD screen, folate/vitamins)
- screening for substance abuse.

Principles Related to Antiretroviral Drug Use by HIV-Positive Pregnant Women and Their Infants

Therapies of known or potential benefit should not be withheld during pregnancy unless:

- there are known adverse effects on the mother, fetus or infant; and
- these side effects outweigh potential benefit to the woman.

Special considerations regarding drug choice would be: a) antiretroviral pharmacokinetics in pregnancy, and b) potential toxicities to pregnant woman and/or her fetus.

A decision regarding use of antiretrovirals during pregnancy should be made by the woman following discussion of known and unknown benefits and risks. The discussion should include information on:

- AZT efficacy for reducing transmission
- antiretrovirals recommended for her own health
- relationship between transmission and HIV RNA
- potential efficacy of elective cesarean delivery in reducing transmission
- unknown long-term risks of in utero exposure.

A long-term treatment plan should be developed for the woman and follow-up planned for the infant. Providers should also discuss general preventable risk factors for transmission (drug use, smoking, multiple sexual partners).

It is strongly recommended that health care providers who are treating HV-1 infected pregnant women and their newborns report cases of prenatal exposure to antiretroviral agents (either alone or in combination) to the Antiretroviral Pregnancy Registry, whose purpose is assess the potential teratogenicity of these drugs (phone 800-258-4263 or fax 800-800-1052).

General Considerations in Therapeutic Decision-Making for HIV-Positive Pregnant Women

General considerations in therapeutic decision-making for HIV-positive pregnant women include:

- gestational age of pregnancy
- HIV RNA level
- CD4 cell count
- clinical stage
- antiretroviral treatment history
- prevention of perinatal transmission
- safety/toxicity for mother and infant.

Special Considerations on Antiretroviral Drug Use by HIV-Positive Pregnant Women and Their Infants

Special considerations on antiretroviral drug use by HIV-positive pregnant women and their infants should include:

- drugs with higher teratogenic risk (efavirenz, hydroxyurea)
- combination antiretroviral therapy and preterm delivery (conflicting data)
- protease inhibitors and hyperglycemia
- mitochondrial toxicity and nucleoside analogues:
  - pregnancy – lactic acidosis, hepatic steatosis, pancreatitis (d4T/ddI fatalities)
  - fetus/infant – theoretical mitochondrial toxicity with in-utero exposure
    - Blanche S, et al. "Possible mitochondrial dysfunction and perinatal exposure to nucleoside analogues." *Lancet* 1999;354:1084-9.
    - Perinatal Safety Review Working Group. "Lack of death due to mitochondrial disease in children who died at <5 years in 5 U.S. cohorts." *JAIDS* 2000;25:261-8.

Following are various scenarios related to antiretroviral prophylaxis

Antiretroviral Prophylaxis Scenario 1: HIV-positive pregnant women who have not received prior antiretroviral therapy

- Conduct standard clinical, CD4 and RNA evaluations.
  - Blattner W. "Delivery plasma HIV RNA levels and perinatal transmission in WITS, 1990-1999." *XIII AIDS Conf*, July 2000, Durban S Africa (LBOr4)
  - Ioannidis JPA, et al. "7-Cohort meta-analysis of transmission from mothers with delivery HIV RNA <1,000." *J Infect Dis* 2001;183(4):539-45.
- 3-part 076 AZT regimen recommended to reduce perinatal transmission.
- Combine AZT prophylaxis with additional drugs to treat HIV infection:
  - Recommend for women whose clinical, CD4 or RNA status requires treatment.
  - Strongly consider for any woman with RNA >1,000.
- Women in 1st trimester may consider delaying therapy until after 10-12 weeks gestation.

Antiretroviral Prophylaxis Scenario 2: HIV-positive pregnant women receiving antiretroviral therapy during the current pregnancy

- If pregnancy identified after 1st trimester, continue therapy.
- If pregnancy identified during 1st trimester, discuss risks/benefits; if discontinue, all drugs should be stopped and restarted at same time.
- AZT should be a component of regimen after 1st trimester whenever possible.
- AZT is recommended intrapartum and to newborn regardless of maternal antenatal regimen.
- Resistance testing recommendations same as for non-pregnant (acute infection, virologic failure).
- The addition of intrapartum/newborn nevirapine is not recommended for women already receiving antenatal antiretroviral treatment who still have detectable viral load, as data from a clinical trial does not indicate this offers additional benefit in reducing transmission and has a risk of inducing nevirapine resistance.
  - Dorenbaum A. "Transmission in PACTG 316 by treatment arm.". *8th Retrovirus Conf*, Feb 2001, Chicago, IL (Abstract LB7)
  - Sullivan J. "PACTG 316: NVP resistance in women receiving ARV treatment with delivery HIV RNA >3,000." *XIII AIDS Conf*, July 2000, Durban, S. Africa (LbOr014).

Antiretroviral Prophylaxis Scenario 3: HIV-positive pregnant women in labor who have had no prior antiretroviral therapy

- Several intra-/postpartum regimens are available:
  - 2-dose nevirapine
  - AZT/3TC
  - AZT
  - 2-dose nevirapine plus AZT
- In immediate postpartum period, standard assessments (CD4, RNA) should be performed to determine whether antiretroviral therapy should be recommended for treatment of HIV disease.

Scenario 3:
Intrapartum/Postpartum Prophylaxis Regimens

Drug	Source of Evidence	Regimen	Efficacy
Nevirapine	HIVNET 012, SAINT	IP: 1 dose onset labor PP: 1 dose infant 48 hrs	47% reduction (vs ultrashort AZT)
AZT/3TC	PETRA, SAINT	IP: Oral PP: Infant 1 wk	38% reduction
AZT	Observational (Wade, Fiscus)	IP: Intravenous PP: Infant 6 wks	62% reduction
AZT/ Nevirapine	Theoretical	Combine Nevirapine and AZT regimen	?

Antiretroviral Prophylaxis Scenario 4:Infants born to HIV-positive women with no therapy during pregnancy or intrapartum

- 6-week neonatal AZT prophylaxis recommended.
- AZT should be initiated within 6-12 hours of birth; after 48 hours it is unlikely to be effective.
  - Wade NA, et al., "Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus." *N Engl J Med* 1998; 339:1409-14.
- Some clinicians may choose to give AZT combined with other antiretrovirals, but efficacy unknown and appropriate dosage and safety incompletely defined.
- In immediate postpartum period, standard assays (CD4, RNA) should be performed to see whether antiretroviral therapy recommended for mother.
- Infant should have early diagnostic testing to allow early treatment if found to be infected.

Elective Cesarean Section to Prevent Perinatal Transmission

A recent European study suggested that delivery by elective cesarean section (C/S) may reduce vertical transmission of HIV (European Mode of Delivery Collaboration. "European randomized mode of delivery trial: elective cesarean at 38 weeks vs. vaginal delivery." *Lancet* 1999;353:1035-9). Similarly, a meta-analysis of 15 cohort studies showed elective C/S reduced the risk of transmission by 50% in women not receiving antiretrovirals and by 70% in women receiving AZT prophylaxis (International Perinatal HIV Group. "The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1--a meta-analysis of 15 prospective cohort studies." *New England Journal of Medicine* 1999 Apr 1;340(13):977-87). Elective C/S is defined as C/S occurring PRIOR TO labor and/or rupture of membranes. Four possible mode-of-delivery scenarios are presented here:

Mode-of-Delivery Scenario A: HIV-positive woman >36 wks gestation, no ARV therapy, HIV RNA/CD4 pending but unlikely available before delivery

- Start antiretroviral therapy, including at least AZT.
- Discuss therapy options.
- Counsel elective C/S likely to reduce transmission.
- Inform C/S risks (surgical, anesthesia, post-op infection).
- Schedule C/S at 38 weeks gestation.
- Intrapartum IV (start 3 hours before C/S) and infant 6 week AZT should be given.
- Discuss options to continue or start combination antiretrovirals postpartum once RNA/CD4 return.

Mode-of-Delivery Scenario B: HIV-positive woman starting HAART 3rd trimester with initial viral response but HIV RNA substantially >1,000 copies/ml at 36 weeks gestation

- Continue HAART, as RNA level dropping appropriately.
- Counsel that unlikely RNA will be <1,000 by delivery.
- Therefore, elective C/S may provide additional benefit in reducing intrapartum transmission to infant.
- Inform C/S risks.
- Intrapartum and infant 6-week AZT should be given.

- Continue other antiretrovirals on schedule as much as possible before/after surgery.
- Emphasize importance of HAART adherence.

Mode-of-Delivery Scenario C: HIV-positive woman on HAART with HIV RNA level undetectable at 36 weeks gestation

- Continue HAART.
- Counsel that risk transmission when on ARV and with persistent undetectable RNA is low (<2%), even with vaginal delivery.
- There is currently no information to evaluate whether elective C/S will substantially lower risk further.
- C/S has increased risk of complications for woman compared to vaginal delivery, which should be balanced against uncertain benefit of C/S in this case.
- Intrapartum and infant 6-week AZT should be given.

Mode-of-Delivery Scenario D: HIV-positive woman with planned elective C/S but who present early in labor or shortly after membrane rupture

- Start IV AZT immediately since woman in labor and/or ruptured membranes
- If labor progressing rapidly, allow vaginal delivery.
- If cervical dilatation minimal and long labor anticipated, some clinicians may choose to give AZT IV loading dose and proceed with C/S to minimize duration membrane rupture and avoid vaginal delivery.
- Others might begin pitocin augmentation to enhance contractions and potentially expedite delivery; avoid invasive procedures (e.g., scalp electrodes).
- Infant should receive 6 weeks of AZT.

Virologic, Immunologic and Other Monitoring During Pregnancy

During the pregnancy of HIV-infected women, providers should monitor:

- CD4 count: same as non-pregnant.
  - baseline (diagnosis pregnancy), q 3-4 months
- HIV RNA: same as non-pregnant.
  - baseline (diagnosis pregnancy), prior to therapy, 4 weeks after start/change therapy, q 3-4 months.
- resistance testing: same as non-pregnant
  - acute infection or virologic failure
- additional monitoring based on antiretroviral drug:
  - NRTI – lactic acidosis, hepatic steatosis
  - NNRTI – rash, hepatitis
  - PI – hyperglycemia, preterm delivery (?)

Monitoring of the Newborn
Monitoring of the newborn should include:

- CBC: minimum monitoring for hemoglobin/ neutrophil count:
  ---- at birth/baseline
  ---- 6 weeks
  ---- 12 weeks
  ---- more frequent if anemic at birth or premature
- If other antiretrovirals are given, more frequent or intensive (e.g., liver function tests) monitoring may be warranted.
- PCP prophylaxis:
  ---- initiate at age 4-6 weeks
- HIV virologic diagnostic testing:
  ---- birth – 48 hours
  ---- 2 weeks
  ---- 1-2 months (after chemoprophylaxis finished)
  ---- 3-6 months.